THE BULLETIN OF Mathematical BIOPHYSICS

JUNE 1944

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BULLETIN OF
MATHEMATICAL BIOPHYSICS
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A NOTE ON THE MATHEMATICAL BIOPHYSICS OF AMEBOID MOVEMENTS

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Theoretical considerations lead to the expectation of some regularities in the apparently random changes of shape of an ameba. We should expect quasiperiodic fluctuations of the ratio of the perimeter to the area of the optical cross-section of an ameba, when plotted against time. The quasi-period should be characteristic of the species. Preliminary experiments appear to bear out that prediction.

This note describes preliminary results of a research problem, planned originally on a larger scale. Due to the present emergency and the duty in the Armed Forces of one of the authors (R. B.), the work has been temporarily discontinued. However, the preliminary results obtained appear of sufficient interest to warrant this note.

A few years ago one of the authors (Rashevsky, 1939) showed mathematically that under the influence of the diffusion drag forces a cell may exhibit either periodical or quasiperiodical changes of shape, by alternately elongating and contracting. It was suggested then, that a similar mechanism may underlie the protrusion and retraction of a pseudopod. In an actual case the presence of a large number of disturbing factors may obliterate the quasiregularity of the phenomenon, and at first glance it may appear to be devoid of any such regularity. In the case of a simple elongation and contraction of a cell, the ratio of length to width of the cell is the natural quantity whose variation with time could be studied. In a moving ameba such quantities are sometimes not defined at all. The difficulty may, however, be overcome.

An elongation of a regularly shaped cell is always accompanied by an increase of the specific surface. If we consider axially symmetric cells, then an elongation also consists of an increase of the ratio of the perimeter of the meridional cross-section to its area. For a cylindroid cell of length $2r_1$ and width $2r_2$ that perimeter is equal approximately to

$$p = 4(r_1 + r_2), \tag{1}$$

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while the area of the meridional cross-section is equal to

$$s = 4\, r_1\, r_2\,. \tag{2}$$

Since for a constant volume V_0 of the cylindroid cell

$$2\pi r_1 r_2^2 = V_0 = \text{const.} \tag{3}$$

therefore, putting

$$\sqrt{V_0/2\pi} = a\,, \tag{4}$$

we have

$$\frac{p}{s} = \frac{r_1^{3/2} + a}{a r_1} = \frac{(r_1/r_2) + 1}{a^{2/3}\,(r_1/r_2)^{2/3}}. \tag{5}$$

Hence if r_1/r_2 fluctuates, so will also p/s, and if for a constant V_0 we know either one of the quantities p/s, r_1 or r_1/r_2, we know the other two.

The quantity p/s has the advantages of being independent on the shape and relatively easily determined. In a cell of regular shape we may observe r_1/r_2 directly. In an irregularly shaped cell we may observe p/s and *define* r_1 or r_1/r_2 from equations (5).

If the apparent lack of regularity in the ameboid movements is due to disturbing factors, which affect strongly the details of the shape, but do not upset fundamentally the mechanism of elongation and contraction, we may expect that the quantity p/s will exhibit quasiperiodic fluctuations, even though we cannot define such quantities as length or width. A true periodicity is not likely, since the disturbing factors will affect also the length of the period. By plotting p/s against time we should, however, expect a fluctuating curve, in which the distances between successive maxima or minima, while not equal, scatter around a constant value. That value, which may be tentatively identified with the theoretical period, should depend on the physicochemical constants of the cell, and be a characteristic of the species.

To test this expectation photomicrographs of several amebas (*Amoeba proteus, Chaos chaos* and a limax type) were taken at regular intervals of the order of a minute. The perimeters and areas were then measured on the enlarged photographs. The perimeters were first measured with a map measure, the areas with a planimeter. Subsequently an apparatus has been devised consisting of a combined planimeter and a pantograph. The long arm of the pantograph carries a vertical graduated capillary filled with ink and makes an enlarged tracing of the cross-section as the point of the planimeter is moved along the original photograph. The amount of ink drawn from the capillary measures the length of the perimeter, while the reading of the planimeter multiplied by an appropriate constant, gives the area.

FIGURE 1

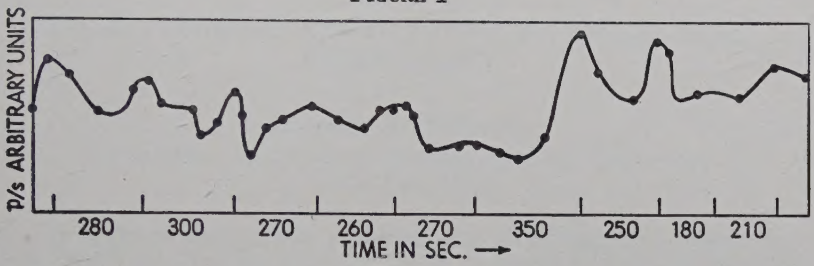

Figure 1 represents a sample of a curve obtained by plotting p/s against time for an ameba of the limax type. The intervals between the maxima are in seconds—280, 300, 270, 260, 270, 350, 250, 180, 210, 300, (the last interval is not shown in the figure) with an average of 267 sec., and a standard deviation of 47.6 sec. Another similar set of measurements, made at a different time, gave a quasiperiod of 269 sec., with a standard deviation of 85 sec.

Similar curves were obtained for *Amoeba proteus* and *Chaos chaos*. The values of the quasi-periods are correspondingly 173 sec. s.d. 86.6 sec.; and 9.41 min. s.d. 3.8 min.

While no definite conclusions can yet be drawn from those preliminary studies, they seem to indicate that even the motion of amebas, almost the classical example of something chaotic and random, may be described quantitatively and mathematically.

This work has been aided in part by a grant from Dr. Wallace O. and Clara A. Abbott Memorial Fund of the University of Chicago.

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BULLETIN OF
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ON A POSSIBLE MECHANISM FOR BIOLOGICAL PERIODICITY

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It is shown that osmotic coupling between solutes, leads, under certain conditions, to differential equations of penetration which have periodic solutions. One such set of conditions is that the permeating solutes have very similar colligative properties, but that their concentrations in the external medium be quite different. It is noted that isotopes may satisfy these conditions exactly, and that they have been observed experimentally to penetrate as predicted. The differential equations bear a resemblance to the interactive equations of Volterra and Lotka.

Certain reaction-systems have from time to time been proposed to account for at least some observed biological periodicities. The analysis of one of these has been given quite completely by A. Weinberg (1938, 1939) and N. Rashevsky (1938, p. 54), namely the coupling

$$\begin{aligned} dc_1/dt &= a_{11}c_1 + a_{12}c_2 \,, \\ dc_2/dt &= a_{21}c_1 + a_{22}c_2 \,, \end{aligned} \tag{1}$$

which has the physical interpretation of *mutual catalysis without combination.* A second system was proposed by A. J. Lotka long ago (Lotka, 1910, 1920),

$$\begin{aligned} dc_1/dt &= c_1(a_{11} + a_{12}c_2), \\ dc_2/dt &= c_2(a_{22} + a_{21}c_1). \end{aligned} \tag{2}$$

Originally, Lotka gave the system (2) the interpretation of two consecutive irreversible reactions in which the first substance catalyzed its own decomposition. In this guise, Lotka realized that the connection with reality was quite remote.* At least to some extent, reaction-system (1) is subject to the same criticism as Lotka's original hypothesis. Catalytic systems seem invariably to feature the formation of intermediates, and their analysis is plagued by corresponding difficulties.

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* *Loc cit.*, p. 274. Later, however, in the hands of Lotka and Volterra, the system (2) took on the highly significant interpretation of interaction between predator and prey species, and in this form it was experimentally verified by G. F. Gause.

In attempting to study the simplest cases of penetration of membranes under general thermodynamic conditions, the author was led to equations which in a sense are referable to equations (2), and which in certain cases may explain periodic or oscillatory penetration. These relations seem justifiable by elementary thermodynamic reasoning.

Consider the binary system of substances 1 and 2. For the chemical potentials of these components we have,

$$\begin{aligned} \mu_1 &= \mu^*_1 + RT\log c_1 + \alpha_1 c_2 , \\ \mu_2 &= \mu^*_2 + RT\log c_2 + \alpha_2 c_1 , \end{aligned} \tag{3}$$

where α_1 and α_2 are constants, and the remaining symbols have their usual meanings.

The inclusion of the terms $\alpha_2 c_1$ and $\alpha_1 c_2$ may be argued in the following way. The expression for μ_1 contains a term which represents the work done in bringing one mole of substance 1 from infinity into the solution. This work in general depends on the presence of the other solute, substance 2, and therefore is a function $f(c_2)$ of c_2. For not too large values of c_2 we may expand $f(c_2)$ and retain only the linear term, $\alpha_1 c_2$. The constant term of the expansion is included in μ^*_1. A similar argument applies to $\alpha_2 c_1$.

From equations (3) we have for the force of diffusion on, say, the first component,

$$\vec{F}_1 = -\nabla \mu_1 = -\frac{RT}{c_1} \nabla c_1 - \alpha_1 \nabla c_2 , \tag{4}$$

whence the current of diffusion is,

$$\vec{i}_1 = D_1 c_1 \vec{F}_1 = -D_1 (RT \nabla c_1 + \alpha_1 c_1 \nabla c_2).$$

and the penetration over the vector surface, $\vec{S}$, is

$$\vec{S} \cdot \vec{i}_1 = D_1 c_1 \vec{F}_1 \cdot \vec{S} = -D_1 \vec{S} \cdot (RT \nabla c_1 + \alpha_1 c_1 \nabla c_2). \tag{5}$$

The quantity D_1 is not the diffusion coefficient, but is proportional to it. For the sake of simplicity we henceforth consider motion parallel to the x-axis only. We then have the single scalar equation,

$$S_x i_x = -D_1 \left(RT \frac{\partial c_1}{\partial x} S_x + \alpha_1 c_1 \frac{\partial c_2}{\partial x} S_x\right) , \tag{6}$$

with S_x as the area normal to the x-axis. Let us imagine that the membrane to be penetrated is a homogeneous and isotropic barrier of thickness δx and of a phase distinct from the two regions which it separates. These two regions, however, (corresponding to exterior and interior of the cell) we regard as being the same type of phase, to follow the customary procedure. Let the partition coefficients between the membrane substance and the two regions be p_1 and p_2 respectively for substances 1 and 2. Under these circumstances we can approximate $\partial c_1/\partial x$ and $\partial c_2/\partial x$ *across the membrane.* (See Figure 1.)

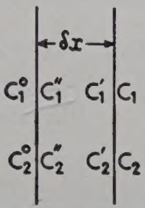

FIGURE 1

Taking, for instance, $c^0{}_1 \mid c''{}_1$ as the concentrations at the immediate exterior-membrane interface, and $c'{}_1 \mid c_1$ as the concentrations at the *immediate* membrane-interior interface, we may write approximately,

$$\left(\frac{\partial c_1}{\partial x}\right)_{\text{membrane}} \cong \frac{c''{}_1 - c'{}_1}{\delta x} = p_1 \frac{c^0{}_1 - c_1}{\delta x},$$

and on substituting into (6),

$$(S_x i_x)_{\text{membrane}} = -D_1 S_x \left(RTp_1 \frac{(c^0{}_1 - c_1)}{\delta x} + \alpha_1 c_1 p_2 \frac{(c^0{}_2 - c_2)}{\delta x} \right) ; \quad (7)$$

or

$$(S_x i_x)_{\text{memb.}} = \frac{-D_1 S_x RTp_1}{\delta x} (c^0{}_1 - c_1) + \frac{-\alpha_1 c_1 p_1 D_1 S_x}{\delta x} (c^0{}_2 - c_2) . \quad (8)$$

It is seen that the doublet,

$$\left\{ \frac{-D_1 S_x RTp_1}{\delta x} , \frac{-\alpha_1 p_2 D_1 S_x}{\delta x} \right\} = \{h_{11} , h_{12}\} , \quad (9)$$

rather than the usual h_{11}, characterizes the permeability of the membrane.

Combining equations (4), (8), and (9), we are led to the two differential equations,

$$\begin{aligned} dc_1/dt &= h_{11}(c^0{}_1 - c_1) + h_{12}\, c_1 (c^0{}_2 - c_2), \\ dc_2/dt &= h_{22}(c^0{}_2 - c_2) + h_{21}\, c_2 (c^0{}_1 - c_1). \end{aligned} \tag{10}$$

Assuming that the external concentration of these substances is sensibly constant, we may write,

$$\begin{aligned} dc_1/dt &= a_{11}\, c_1 + a_{12}\, c_1\, c_2 + a_{13}\,, \\ dc_2/dt &= a_{22}\, c_2 + a_{21}\, c_2\, c_1 + a_{23}\,, \end{aligned} \tag{11}$$

with

$$\begin{aligned} a_{11} &= h_{12}\, c^0{}_1 - h_{11}\,, & a_{22} &= h_{21}\, c^0{}_2 - h_{22}\,, \\ a_{12} &= -h_{12}\,, & a_{21} &= -h_{21}\,, \\ a_{13} &= h_{11}\, c^0{}_1\,, & a_{23} &= h_{22}\, c^0{}_2\,. \end{aligned} \tag{12}$$

Let us set $u_1 = c_1 - a_{13}t$, and $u_2 = c_2 - a_{23}t$. We may then continue formally by substituting into equation (11), and obtain:

$$\begin{aligned} du_1/dt &= a_{11}\, c_1 + a_{12}\, c_1\, c_2\,, \\ du_2/dt &= a_{22}\, c_2 + a_{21}\, c_1\, c_2\,. \end{aligned} \tag{13}$$

Eliminating t by division and rearranging we have,

$$(a_{22}/c_1 + a_{21})\, du_1 = (a_{11}/c_2 + a_{12})\, du_2\,. \tag{14}$$

But in view of our change of variable, this expression is equivalent to:

$$\begin{aligned} &(a_{22}/c_1 + a_{21})\, dc_1 + (a_{11}/c_2 + a_{12})\, a_{23}dt \\ &\qquad = (a_{22}/c_1 + a_{21})\, a_{13}dt + (a_{11}/c_2 + a_{12})\, dc_2\,, \end{aligned}$$

whence, integrating formally, we have:

$$\begin{aligned} &a_{22} \log c_1 + a_{21}c_1 - (a_{11} \log c_2 + a_{12}\, c_2) \\ &\qquad = K + a_{22}a_{13} \textstyle\int_0^t dt/c_1 - a_{11}a_{23} \int_0^t dt/c_2 + (a_{13}a_{21} - a_{12}a_{23})\, t, \end{aligned} \tag{15}$$

with K as a true constant of integration. The equation

$$a_{22} \log c_1 + a_{21}\, c_1 - (a_{11} \log c_2 + a_{12}\, c_2) = K \tag{16}$$

is the integral of the system (2) arrived at by Lotka and Volterra (Lotka, 1910, 1920, 1925, Volterra, 1931, 1935), and shown graphically by these authors to represent a closed curve, thus indicating *undamped* oscillations in time of c_1 and c_2. It is evident that equation (15) can be studied from the point of view of regarding equation (16) as an equation in which K is a function of time.

First, however, it is necessary to consider a simple analytic proof showing that equation (16) represents, indeed, a closed curve. Take the state of affairs when c_2 has a definite value, say ξ. We may write,

$$\Psi(c_1) = \log c_1 + \frac{a_{21}}{a_{22}} c_1 = \frac{K + a_{11} \log \xi + a_{12} \xi}{a_{22}}. \tag{17}$$

$\Psi(c_1)$ has one and only one *maximum* when,

$$1/c_1 + a_{21}/a_{22} = 0\,, \quad \text{or} \quad c_1 = -\,a_{22}/a_{21}\,; \tag{18}$$

$$(\text{since for all } c_1\,,\ d^2\Psi/dc^2{}_1 < 0)\,;$$

whence if there are any solutions at all to (17) there will be one or two, according as,

$$\log\left(-\frac{a_{22}}{a_{21}}\right) - 1 \geqq \frac{K + a_{11} \log \xi + a_{12} \xi}{a_{22}}. \tag{19}$$

If the inequality of (19) holds (as it can be made to do, by proper choice of ξ), then the line $c_2 = \xi$ removes two points from the set of points represented by equation (16), and it follows from the simple relations (18), that the remaining sets are connected. There are therefore two partitions, whence the set (16) is homoeomorphic to a circle, i.e. it is a Jordan curve. (See, for instance, Newman, 1931, page 54).

In view of the relation (19) it follows that the roots of (17) will be far apart or close together according as K is small or large respectively, or more pictorially: as K grows larger, the integral curves represented by equation (16) are reduced in their vertical diameters (and conversely). Let us now return to equation (15), in which "K" is, in effect, a function of time. Successive segments (traced out in time) of the c_1–c_2 curve represented by equation (15) can be regarded as segments of integral curves of (16) whose diameters are being continuously reduced, provided the expression,

$$a_{22}a_{13} \int_0^t dt/c_1 - a_{11}a_{23} \int_0^t dt/c_2 + (a_{13}a_{21} - a_{12}a_{23})\,t \tag{20}$$

increases in time. Under such conditions the curve (15) will have the general property of a *spiral winding inward*, which implies that *c_1 and c_2 are both approaching steady values in time, but approaching them in oscillatory fashion* (*damped oscillations*). We cannot go further with (20) in general terms, except to remark that the two integrals will be determinate throughout, for the concentrations pass from some non-zero value to another non-zero value (steady state).

Let us now see if the increase in time of expression (20) can be assured in some specific case. To do so we must examine the nature of the constants, a_{ij}, in the case to be studied. If substances 1 and 2 are two radioactive isotopes, or at least two rather similar substances, we might reasonably expect that the permeability constants, h, would be of the same order of magnitude. In the isotopic case, it would be proper to equate them, since such properties as diffusion velocity depend only slightly on nuclear structure. Let us take h_{ii} as the principal permeability and h_{ij} as the cross permeability, and let us suppose that the integrals are of the same order of magnitude, say I (as would be the case if the penetration rates were similar). We may then write expression (20) as:

$$-h^2_{ii}I(c^0_1 - c^0_2) - h_{ii}h_{ij}(c^0_1 - c^0_2)t\,,$$

whence if $c^0_1 < c^0_2$ the conditions for the increase of K with time are clearly satisfied. A most suggestive set of experiments, in this connection, is that of S. C. Brooks on the uptake of radio-potassium by *Nitella* (Brooks, 1940). *Normal* potassium is of course penetrating simultaneously, and the external concentration of normal potassium is distinctly greater than that of radio-potassium. The scrupulous care with which such experiments were done argues for the reality of the oscillations observed; and the striking similarity between the observed phenomenon and the rough qualitative predictions given above suggests that the experiments might well be explained by this type of coupled penetration. A more extended analysis of these equations —which it is hoped may be carried out in the future—is necessary before application to other than isotopic cases.

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ON THE THEORY OF CELL DIVISION FROM THE POINT OF VIEW OF THE PRINCIPLE OF MAXIMUM ENERGY EXCHANGE

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An analysis is made of the equation of cellular elongation during division, which was derived by N. Rashevsky from the principle of maximum energy exchange. The method used is the same as that employed by H. D. Landahl in discussing a similar equation deduced from the theory of diffusion drag forces. The differential equation is expanded in a power series of the relative elongation, and in this way is reduced to the form studied by H. D. Landahl, which has been shown to agree very well with experimental data. An estimate of the order of magnitude of the universal constant τ, which appears in the generalized Hamiltonian principle, is made, and τ is found to be of the order of 10^{-4} sec.

Some time ago, N. Rashevsky (1943a) suggested a generalized Hamiltonian principle, applicable to biological phenomena. The usual Hamiltonian principle of physics is obtained as a particular case of the generalized one. As an example of a possible application, Rashevsky has treated the problem of cell elongation during division. The differential equation for cell elongation obtained in this manner looks very similar to the one obtained previously on the basis of diffusion drag forces (Rashevsky, 1940; Landahl, 1942b), and can be shown to give integral curves of a similar shape. The purpose of this paper is to investigate in detail to what extent the new equation of Rashevsky's agrees with data obtained by R. Buchsbaum and R. R. Williamson (1943) for *Arbacia* eggs, which were correctly predicted by H. D. Landahl (1942b) from the old equation. We shall see that Rashevsky's equation can be reduced to the same form to which Landahl reduced the old one.

Denoting by

$r_1 =$ one half of the "length" of the cell
$r_0 =$ radius of the cell when spherical
$c_0 =$ concentration of the single metabolite at great distances from the cell
$D =$ internal diffusion coefficient

V = total volume of the cell

w = heat of reaction per gram of the substance produced

a = constant of proportionality such that the rate of production of the substance is equal to $a\bar{c}$ with $\bar{c}$ the average internal concentration of the metabolite

τ = universal constant in the Hamiltonian principle

η = average coefficient of viscosity of the cell

γ = surface tension

S = total surface of the cell

Rashevsky's (1943b) elongation equation for a cell may be written

$$\frac{dr_1}{dt} = \frac{2\,VD\,wa^2c_0\tau}{\pi\,\eta} - \frac{(r_1^3 - r_0^3)\,r_1}{[3D\,(2r_1^2 + r_0^3/r_1) + ar_0^3r_1]^2}$$

$$- \frac{4r_1^2\gamma}{9V\,\eta}\,\frac{dS}{dr_1}. \tag{1}$$

The equation discussed previously by Landahl (1942b) is

$$\frac{r_1}{r_1 - r_2}\,\frac{dr_1}{dt}$$

$$= \frac{RTq\,\mu\,r_0^3}{4M\,\eta\,D_e}\,\frac{1}{1 + (1 + b)\,r_0^3/2r_1^3 + br_0^{3/2}/r_1^{3/2}} - \frac{\gamma}{2\,\eta}\left(\frac{r_1}{r_0}\right)^{3/2}. \tag{2}$$

where

$$b = 2\,D_i/D_e; \quad V = 4\,\pi\,r_1\,r_2^2/3 = 4\,\pi\,r_0^3/3\,, \tag{3}$$

with D_i and D_e being the internal and external diffusion coefficients, respectively.

Introducing relation (3) into equation (1) and putting

$$r = r_1\,, \quad a' = a\,r_0^2/6D\,, \quad K_1 = Vwa^2c_0\tau/18\,\pi\,\eta\,D \tag{4}$$

we find

$$\frac{dr}{dt} = K_1\,\frac{r^3 - r_0^3}{r^3[1 - a'\,r_0/r + (r_0/r)^3/2]^2} - \frac{\gamma}{3\,\pi\,\eta}\,\frac{r^2}{r_0^3}\,\frac{dS}{dr}. \tag{5}$$

Similarly, equation (2) may be transformed into

$$\frac{dr}{dt}=K_2\frac{r^{3/2}-r_0^{3/2}}{r^{3/2}[1+b(r_0/r)^{3/2}+(1+b)(r_0/r)^3]}-\frac{\gamma}{2\eta}\frac{r^{3/2}-r_0^{3/2}}{r_0^{3/2}} \tag{6}$$

where

$$K_2=R\,T\,q\,\mu\,r_0^3/4\,M\,\eta\,D_e\,. \tag{7}$$

In equation (5) the denominator in the first term is always positive if $\alpha' < 3/2$ and consequently, the parameters in equation (4) will be restricted according to this condition. The similarity is now apparent between equation (5) and equation (6), provided dS/dr has the proper functional form.

For the determination of the explicit form of dS/dr, Rashevsky (1943b) has suggested two approximations:

I. Approximate the cell shape by an ellipsoid,

$$S=4\pi r_0^2+1.6\pi r_0^2(r/r_0-1)^2; \quad dS/dr=3.2\pi(r-r_0). \tag{8}$$

II. Approximate the cell shape by a cylinder,

$$S=2\pi r_0(r_0r)^{1/2}; \quad dS/dr=\pi r_0(r_0/r)^{1/2}. \tag{9}$$

As a third alternative, one might assume that a dividing cell can be represented by two intersecting spheres whose radii are equal and whose common interior is counted only once. During the elongation process the centers of the spheres will separate and the radii change in such a manner that the total volume enclosed by the composite surface will remain constant.

Calculating the volume and surface of the two spherical segments constituting the cell, and remembering that V, S, r, r_0, refer to the whole cell as defined in the expressions above, it follows that

$$V/2=\pi r^2(R-r/3), \quad S=2\,V/r+4\pi r^2/3$$

where R is the radius of each spherical segment. Since $V=4\pi r_0^3/3$, we may solve for S in terms of r and r_0. The result is

III. $$S=4\pi(2\,r_0^3+r^3)/3r; \quad dS/dr=8\pi(r^3-r_0^3)/3r^2, \tag{10}$$

the last expression being obtained by differentiation. This shape is a closer approximation to the shape found in the biological phenomenon of cell division in the intermediate stages, but the final results of the calculations in this paper are not materially changed by it.

Following Landahl (1942b), put

$$e=\frac{r-r_0}{r_0}. \tag{11}$$

If either expressions (8), (9), or (10) and expression (11) is substituted into equation (5), and the right side of that equation is expanded in a power series in e, the following form of the expansion is found:

$$de/dt = e(A - Be - Ce^2 + De^3) + E \tag{12}$$

where the coefficients A, B, C, D, and E have somewhat different forms depending on which of the approximations I, II, or III are used for dS/dr. They are given by the following relations:

$$\begin{aligned} I.\quad & A = \frac{12K_1}{r_0(3-2a')^2} - \frac{3.2\,\gamma}{3\,\eta\,r_0}; \qquad B = \frac{6.4\,\gamma}{3\,\eta\,r_0}; \quad E = 0; \\ & C = \frac{4K_1(15+2a')}{r_0(3-2a')^3} + \frac{3.2\,\gamma}{3\,\eta\,r_0}; \qquad D = \frac{4K_1(21+2a')}{r_0(3-2a')^3}. \end{aligned} \tag{13}$$

$$\begin{aligned} II.\quad & A = \frac{12K_1}{r_0(3-2a')^2} - \frac{\gamma}{2\,\eta\,r_0}; \qquad B = \gamma/8\,\eta\,r_0; \\ & E = -\frac{\gamma}{3\,\eta\,r_0}; \\ & C = \frac{4K_1(15+2a')}{r_0(3-2a')^3} - \frac{\gamma}{48\,\eta\,r_0}; \qquad D = \frac{4K_1(21+2a')}{r_0(3-2a')^3} \\ & \qquad - \frac{\gamma}{128\,\eta\,r_0}. \end{aligned} \tag{14}$$

$$\begin{aligned} III.\quad & A = \frac{12K_1}{r_0(3-2a')^2} - \frac{8\,\gamma}{3\,\eta\,r_0}; \qquad B = \frac{8\,\gamma}{3\,\eta\,r_0}; \quad E = 0; \\ & C = \frac{4K_1(15+2a')}{r_0(3-2a')^3} + \frac{8\,\gamma}{9r_0}; \qquad D = \frac{4K_1(21+2a')}{r_0(3-2a')^3}. \end{aligned} \tag{15}$$

As Landahl (1942b) has shown, equation (6) also reduces to the form of equation (12), but with $E = 0$. Not as many terms were retained in Landahl's calculations, and since in cell division, the maximum value which e may have is 0.6, the term involving e^4 may be dropped except for values of a' very close to 3/2.

Equation (12) has been shown by Landahl (1942b) to represent very well the data obtained experimentally for the elongation during division of *Arbacia* eggs. Hence, equation (1) derived from the generalized Hamiltonian principle is shown to agree with those data to the same extent as equation (2), from which the data were actually predicted.

The expansion (12) together with numerical values of the coefficients A, B, and C as calculated by Landahl (1942b) for *Arbacia* eggs makes it possible to evaluate approximately the universal constant τ which enters into the generalized Hamiltonian principle (Rashevsky, 1943a). The average values obtained by Landahl are

$$A = 0.023; \quad B = 0.052; \quad r_0 = 3.4 \times 10^{-3}\,\text{cm}. \tag{16}$$

It is also necessary to assume plausible values for many of the other physical and chemical quantities listed at the beginning of this discussion. Some of them have been evaluated by Landahl (1942b), and others of a more purely physical and chemical nature have been determined experimentally. It is first necessary to examine numerically the magnitude of the constant a' as defined in equation (4) as a check on the validity of the expansions. Considering that for *Arbacia* eggs the total reaction rate $a\bar{c}$ is of the order 10^{-7} gm.cm.$^{-3}$ sec.$^{-1}$ (Rashevsky, 1940), we have with $\bar{c} \backsim 10^{-4}$ gm.cm.$^{-3}$, $a \backsim 10^{-3}$ sec.$^{-1}$. As a biologically plausible value for D we shall put $D \backsim 10^{-7}$ cm.^{2} sec.$^{-1}$ (Rashevsky, 1940). We then have $a' \backsim 10^{-2}$, and consequently, the expansion is valid, and furthermore, we may completely suppress the quantity $2a'$ in comparison with 3 in the equations of the coefficients.

If equation (13), (14), and (15) are solved for the constant K_1 in terms of the coefficients, the results for the three cases are

$$\begin{array}{ll} \text{I} & K_1 = 0.75\, r_0 (A + B/2) = 12.5 \times 10^{-5}, \\ \text{II} & K_1 = 0.75\, r_0 (A + 4B) = 59 \times 10^{-5}, \\ \text{III} & K_1 = 0.75\, r_0 (A + B) = 19.1 \times 10^{-5} \end{array} \tag{17}$$

the numerical values following from equation (16).

Having evaluated the constant K_1, we may now calculate the value of the universal constant τ from equation (4), although plausible values must be assumed for some of the constants entering into the relation. The volume V of the cell can be calculated from relation (3), since r_0 is known, and has the value 1.64×10^{-7} cm.^{3} The external concentration c_0 is higher, but of the same order of magnitude as $\bar{c}$, hence, we may take $c_0 \backsim 10^{-4}$ gm.cm.$^{-3}$. The heat of reaction w in ergs per gram may be estimated from known heats of reaction for a large variety of organic compounds. For the pure hydro-carbons, w does not change widely for compounds with large numbers of carbon and hydrogen atoms ($\backsim$ 50 atoms to the molecule). If the molecule includes oxygen atoms, the heat of reaction is generally lowered somewhat depending on the relative proportion of oxygen in the molecule, and consequently, an average value must be assumed for the quantity

w. We shall take $w \sim 10^{11}$ ergs per gm.

Solving equation (4) for τ we obtain

$$\tau = \frac{18 \pi D K_1 \eta}{V w a^2 c_0} = 3.44 K_1 \eta , \tag{19}$$

and for the three approximations,

$$\begin{array}{ll} I. & \tau = 4.3 \times 10^{-4} \eta \text{ sec.} \\ II. & \tau = 20.3 \times 10^{-4} \eta \text{ sec.} \\ III. & \tau = 6.6 \times 10^{-4} \eta \text{ sec.} \end{array} \tag{20}$$

Following Landahl's discussion (Landahl, 1942c), we may take as a plausible value $\eta \sim 10^{-1}$ cm.^{2} sec.$^{-1}$. This gives for τ the order of magnitude

$$\tau \sim 10^{-4} \text{ sec.} \tag{21}$$

In view of the uncertainty of the values of the constants used in evaluating τ, the value above must be taken with great caution. If τ is of that order of magnitude, then in order for the "energy flow" term in the Hamiltonian to become comparable with the regular "energy" term, the changes in *energy flow* must be at least a thousand times as large as the changes in *energy*, when the configuration of the system is altered. In the inorganic world such systems have as yet not been observed.

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BULLETIN OF
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A NOTE ON NEURAL NETS

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A neural mechanism is described which provides for a perception which is invariant with respect to movement of the stimulus.

Consider a net in which a neuron N is stimulated equally by each of a large group of equivalent neurons whose afferents are spread out uniformily over some surface. Let some part A of this area be subjected to a suddenly applied constant stimulation. If the surface density of the afferent endings is δ, then the total stimulation $\sigma(t)$ acting upon N at time t measured from the application of the stimulus will be given by

$$\sigma(t) = A\,\delta[\varepsilon_0 e^{-at} + j_0 e^{-bt} + \phi(1 - e^{-at}) - \psi(1 - e^{-bt})] \qquad (1)$$

where ϕ and ψ are constants, provided that all the afferents have the same values of ε and j initially.

Suppose now, that instead of the stimulus being applied to a fixed group of the afferent neurons, the stimulus is moved over the area in any manner subject to the condition that the total number of neurons stimulated is constant. This requirement is essentially the same as requiring only that the area stimulated remain constant. Any movement of this sort can be broken down into a process in which a neuron which has been stimulated is removed from the stimulated group just as an unstimulated neuron is added to the group of stimulated neurons. Then we will have shown that $\sigma(t)$ is independent of any movement of the stimulus if it can be shown that when two equivalent neurons are stimulated in immediate succession, the total σ produced at any instant by them is the same as that due to either one being stimulated continuously.

Thus, consider two neurons, the first stimulated in the interval $0 < t < \tau$, and the second in the interval $\tau < t$, τ being arbitrary. If each neuron has initial values ε_0 and j_0, then for $0 < t < \tau$,

$$\sigma(t) = 2\,\varepsilon_0 e^{-at} - 2\,j_0 e^{-bt} + \phi(1 - e^{-at}) - \psi(1 - e^{-bt}), \qquad (2)$$

while for $t > \tau$,

$$\sigma(t) = \sigma(\tau) e^{-a(t-\tau)} + \phi(1 - e^{-a(t-\tau)}) - \psi(1 - e^{-b(t-\tau)}). \qquad (3)$$

But equations (3) and (2) are identical, as can be shown by simple substitution of $\sigma(\tau)$ from (2) into (3), and thus the argument is completed.

If the stimulus, instead of being constant varies with time, one can obtain an expression for $\sigma(t)$ due to the two neurons, in the interval $t > \tau$, the expression (2) plus the term

$$ae^{-at}\int_{\tau}^{t} e^{at}[\phi(t-\tau) - \phi(t)]dt$$

and less an analogous term with a and ϕ replaced by b and ψ. These terms vanish only if the stimulus is constant or periodic and of period τ. Thus, if a number of neurons are arranged in a line, then movement would produce no change in $\sigma(t)$ only if the stimulus is constant, and a constant movement would produce no change in $\sigma(t)$ if the stimulus is periodic with time and moves with the particular velocity given by the interneural distance divided by the period.

The bearing of the above on the theory of the "Gestalt" is apparent.

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EQUIVALENCE OF THE THEORIES OF NERVOUS EXCITATION OF HILL, MONNIER, AND RASHEVSKY

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New and direct proofs of the equivalence of the three theories of nervous excitation are developed, and by the introduction of the *Hauptnutzzeit* as the unit of time and a special unit for the measurement of the excitatory state, a normal form for Rashevsky's equations is obtained which exhibits clearly the relations among the various independent parameters.

The equivalence of Hill's and Rashevsky's theories of nervous excitation has been demonstrated in several ways by Offner (1937), Young (1937), and Householder (1939). The following demonstration seems to possess certain advantages of simplicity and directness.

If we write x_1 and x_2 (or y_1 and y_2) instead of ε and j, the most general two-factor linear theory of excitation may be written, in matrix form,

$$x' = a(x - x^0) + \alpha S\,, \tag{1}$$

where $x' = dx/dt$, x, x^0 and α are column vectors, a is a 2×2 matrix, and S, the measure of the stimulus, is a scalar. Excitation occurs when

$$x_1 \geqq x_2\,, \tag{2}$$

and if

$$x = cy\,, \tag{3}$$

the transformed equations

$$y' = b(y - y^0) + \beta S \quad (b = c^{-1} ac\,, \beta = c^{-1} \alpha) \tag{4}$$

represent an equivalent theory provided the relations (2) and

$$y_1 \geqq y_2 \tag{5}$$

are simultaneously satisfied. Evidently, c must have the form

$$c \begin{pmatrix} r + r_1 & r_2 \\ r_1 & r + r_2 \end{pmatrix}, \; r > 0\,, \tag{6}$$

as is evident when equation (3) is written in scalar form. But if the matrix b is to be a diagonal matrix (Rashevsky's form), then the diagonal elements of b must be the characteristic roots $-\mu_1$ and $-\mu_2$ (necessarily negative) of the matrix a, and the columns r^1 and r^2 of c must satisfy

$$ar^i = -\mu_i r^i , \tag{7}$$

as is well-known and easily verified. We may take r to be any positive number, after which choice the transformation is unique.

As a possibility for the further normalization of the equations, we note that they now have the form

$$y'_i + \mu_i(y_i - y_i^0) = \beta_i S . \tag{8}$$

A change in the unit of time

$$\tau = t/T$$

replaces μ_i and β_i by $T\mu_i$ and $T\beta_i$. A natural unit of time is that required for rheobasic stimulation. If this is assumed in equation (8), it follows that, since stimulation occurs at $t = 1$ (in the units of time now employed),

$$\beta_1/\beta_2 = e^{\mu_1}/e^{\mu_2}$$

or

$$\beta_1 = \kappa\, e^{\mu_1}, \quad \beta_2 = \kappa\, e^{\mu_2}.$$

We may then choose the units for y so that $\kappa = 1$ and have

$$y'_i + \mu_i(y_i - y_i^0) = Se^{\mu_i}. \tag{9}$$

Since the measure of the y enters only through the ratio of the difference $y_2^0 - y_1^0$ to a measure of some particular form of stimulation, say the rheobasic constant current, the four intrinsic parameters are exhibited as this ratio, the unit of time, and the parameters μ_i. Hill introduces the further restriction of assuming normal accommodation which reduces the parameters to only three and we are able to write

$$\mu_1 = \frac{\lambda}{\lambda - 1}\log\lambda, \quad \mu_2 = \frac{1}{\lambda - 1}\log\lambda, \qquad \lambda = \mu_1/\mu_2 . \tag{10}$$

The reduction of Rashevsky's equations to a single second-order equation (Monnier's form) is most easily effected if we write ε and j in place of Rashevsky's $\varepsilon - \varepsilon_0$ and $j - j_0$. Rashevsky's differential equation may be written in operational form

$$\begin{aligned}(D + k)\varepsilon &= KI ,\\ (D + m)j &= MI ,\end{aligned} \qquad (D = d/dt). \tag{11}$$

With a suitable choice of the units for ε and j, the condition for excitation may be written

$$\varepsilon - j \geqq 1. \tag{12}$$

If we operate upon the first of equations (11) by $(D + m)$, upon the second by $(D + k)$, and subtract, we have

$$\begin{gathered} \sigma \equiv \varepsilon - j, \\ d^2 \sigma/dt^2 + (k + m) d \sigma/dt + k m \sigma \\ = (K - M) d I/ dt + (m K - k M) I. \end{gathered} \tag{13}$$

To obtain the initial conditions, σ_0 and σ_0', we note that a discontinuity in $I(t)$ in amount ΔI results in proportional discontinuities in ε', j', and σ' but not in ε, j, or σ. The discontinuity in σ' is easily found to be

$$\Delta \sigma' = (K - M) \Delta I. \tag{14}$$

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BOOK REVIEW

JOSEPH NEEDHAM. *Biochemistry and Morphogenesis.* 1942. xvi + 787 pp. Cambridge: At the University Press; New York: The Macmillan Company. $12.50.

The vegetative activity of cellular aggregates has received but scant consideration from the point of view of mathematical biophysics, Rashevsky's theory of gastrulation being the only instance. The theory of organic form, as developed by the same author, contains no reference to the cellular constitution of the organism, and provides no mechanism for the attainment of the form under consideration, but deals with the end result only. It is to be hoped that some theoretical study may be made in the near future of the physical mechanism involved in morphogenesis.

Needham's book, *Biochemistry and Morphogenesis,* should prove very valuable in providing a stimulus and a background for such studies. While it is true that the author's interest attaches chiefly to the chemical processes, and while there is as yet little apparent physical significance to be found in some of the problems treated, nevertheless, with even a casual reading of the book one finds many places where quantitative theoretical formulations seem called for, and ultimately, chemistry and physics are bound to coalesce, in morphology as elsewhere. From this point of view, the molecular and electronic structures of the various inductors will take on increasing significance as progress is made in the field of morphology and also in the field of theoretical chemistry. All this the author strongly suggests at many points, especially in his discussion of polarity.

The central theme of the book concerns the manner in which the morphogenetic inductors act upon the reacting elements of the developing organism. Thus the book is divided into three parts: The Morphogenetic Substratum, The Morphogenetic Stimuli, and The Morphogenetic Mechanisms. The first deals principally with the chemical constituents of the egg, the nutrient material, and the maternal organs involved in generation and development. The greater part of the third deals with the biochemistry of respiration and metabolism, but opens with a discussion of the dissociability of the processes of growth, differentiation, and metabolism, includes a section on heterauxesis and closes with a discussion of polarity. Heterauxesis, incidentally, is the term which the author recommends for referring to the relations between the rates of growth of different parts of the same organism, relations which are representable by a rectilinear trajectory on a double-logarithmic plot in a very great many instances.

While the third part represents, in a sense, the culmination of the book, the main body of it is contained in the second part. This gives an extensive treatment of the experimental work dealing with morphogenesis, as well as a critical evaluation of the terminology employed by various workers. This second feature is hardly less valuable than the first, since a carefully constructed vocabulary contains already the framework of the science. And if such terms as "competence", "determination", "potency", and the like, are so clearly in need of quantitative, rather than qualitative, treatment that a feeling of impatience is hard to suppress, it is a virtue rather than a defect in the book that the need for quantitative developments should be thus clearly—if not explicitly—indicated.

It is not necessary to comment on the important rôle that must be played in the development of the subject by such a comprehensive outline by an outstanding authority in this field. Mathematical biophysicists in particular, will find it invaluable when they do undertake any work on problems of development.

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